8 EIQ-0397-13573

# The Goodyear Tire & Rabber Company

Akron, Ohio 44316-0001

PDCN: 8896001005 3 March 7, 1997

Certified Mail

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Attn: Section 8(e) Coordinator

Office Of Pollution Prevention and Toxics (OPPT)

U.S. Environmental Protection Agency

401 M Street, S.W.

Washington, DC 20460

Commins No CBI

Dear Ladies/Gentlemen:

Subject:

Supplemental Information Regarding a TSCA Section 8(e) Notice

Reference:

EPA Document Control Number: 8EHQ-96-13573

This submitted does not contain Confidential Business Information.

The Goodyear Tire & Rubber Company is currently sponsoring a study at Research Triangle Institute (RTI) in Research Triangle Pack, NC to examine the reproductive toxic potential of a rubber antioxidant in laboratory rats. The identity of the material is as follows:

Chemical Abstract Name:

1,4- Benzene-liamine, N, N' - mixed Ph and Tolyl derivs.

Chemical Abstract Number: 68953-84-4\*

On February 28, 1997, additional preliminary results from this definitive two-generation reproduction study were given to Goodyear by the study director. These early findings indicated similar responses in F2 litters (increased mortality in offspring) as seen in F1 groups, although the F2 indicated attenuated chemical potency. Additionally, findings of polycystic kidneys were reported in F1 weanlings. No adverse outcome of these renal lesions were observed as F1 animals matured. Microscopic examinations of F2 weanlings and the F2 adult kidneys will be conducted in the near future. Consequently, under the requirements of TSCA Section 8(e), The Goodyear Tire & Rubber Company is providing EPA with the attached copies of RTI's memorandums.



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The study is continuing and upon completion, final reports will be forwarded to the EPA.

My address and telephone number are as follows:

The Goodyear Tire & Rubber Company Department 100D 1144 East Market Street Akron, Ohio 44316-0001 Telephone Number: (330) 796-2362

Sincerely,

Michael W. Smith

Section Manager, Chemical Information

Systems & Regulatory Affairs

MWS/jh s7m3a7

Attachments (3)

# DRAFT

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## RT96-GY1B F<sub>2</sub> Litter Data

Dose	Sperm Positive	Pregnant	Live Litter on PND 0	Litter Still Live <sup>a</sup>
0	26	22	22	20b
120	26	23	22C	22
400	24	20	20	19d
1500	25	24	226	17f

<sup>&</sup>lt;sup>a</sup>One or more pups survived until PND 21 sacrifice or are still alive as of 2-27-97.

bOne dam was found dead on PND 4 and all the pups in one litter were dead or missing and presumed dead by PND 4.

<sup>&</sup>lt;sup>c</sup>One dam delivered a litter of all dead pups.

dOne dam was found dead on PND 3.

eTwo dams delivered litters of all dead pups.

fOne dam died on PND 0, all the pups in two litters were dead or missing and presumed dead by PND 4 and all the pups in two litters were dead or missing and presumed dead by PND 7.



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#### MEMORANDUM

Rochelle W. Tyl, Ph.D.; RTI

Study Director

John Curtis Seely, D.V.M.; PATHCO

Veterinary Pathologist

DATE: January 16, 1997

Kidney Histopathology: Two-Generation Reproductive SUBJECT:

Toxicity Evaluation of Wingstay 100 Administered in

the Feed to CD (Sprague-Dawley) Rats.

RTI Project No. 65C-6429-400; PATHCO 96-89

Gross examination of F1 weanling (PND 21) animals revealed multiple clear cysts in most of the high dose kidneys (males and females). At the sponsor's request, kidneys from 1/sex/litter (randomly chosen) from high, mid and control groups were submitted for histopathology.

Kidney tissue was processed into paraffin blocks, sectioned and stained with H&E. The right kidney was transected while the left kidney was bisected longitudinally. Individual animal histopathology findings by dose and sex are

attached to this report.

Direct treatment-related lesions were associated with the dose-related presence and increased severity of polycystic kidneys. Microscopically, polycystic kidneys were characterized by the presence of renal tubule cysts primarily in the outer medulla but occasionally present in the inner medulla (papillae) and cortex. Most cysts were lined by cuboidal to flattened epithelial cells with little to no surrounding inflammatory reaction. The majority of the cysts appeared empty; however, several contained either red blood cells, mixed inflammatory cells, desquamated tubular epithelial cells or mixtures of the aforementioned cells. advanced cases, a few cysts appeared multiloculated. Renal medullary tubule dilatation, in most cases, accompanied the cystic change but was not diagnosed separately. Although the mechanism of cyst formation was not apparent, it did not appear to be associated with a primary hydronephrotic mechanism.

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Additional lesions noted in control and exposed weanling pups were renal tubule regeneration and dilatation. The pathogenesis of these two spontaneously occuring lesions was unclear. Several small, focal cortical cysts, unrelated to chemical exposure, were also observed.

During this review, renal tubule regeneration was noted to occur both spontaneously and secondarily to the presence of cysts. In general, regeneration was characterized as a focal linear lesion in the cortex, comprising tubular cytoplasmic basophilia, nuclear crowding, and the presence of peritubular mononuclear inflammatory cells. In areas of renal tubule regeneration associated with the presence of treatment-related cysts, slight tubule dilatation was also apparent. During the dose-range study, tubule regeneration was diagnosed along with the polycystic kidneys to indicate the relationship between the presence of cysts and tubule regeneration noted as a secondary response. In this review, evidence of tubule regeneration associated directly with the presence of cysts was also present.

Renal tubule dilatation was noted as a distinct, focal tubule dilatation which was often surrounded by locse connective tissue and mononuclear inflammatory cells. The majority of cases were apparent in the renal cortex. The relationship, if any, between renal tubule regeneration and dilatation was not apparent. It is possible that some cases of dilatation might have arisen in areas of regeneration.



# TWO GENERATION REPRODUCTIVE STUDY WINGSTAY 100

PROJECT NO. 65C-6429-400 PATHCO #96-89

## Histopathology Results From PND 21 Kidneys

#### MALE

DOSE	CONTROL	MID	A CIF
Kidney Exam.	23	20	Section 1997
Normal	14	5	
Regeneration, RT*	4	7	9
Dilatation, RT	4	eg e	on and a second
Cyat		1	Ô
Polycystic Kidney	0	8	10
Minimal	G	7	
Mild	0	વ્યું વર્ષો	
Moderate	O	0	5
Marked	0	O	3
	40.0		•

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DOSE	CONTROL	MID	RIGH
** 1 gw			
Kidney Exam.	22	18	11
Normal	14	- 7	0
Regeneration, RT	3		10
Dilatation, RT	5	4	
Polycystic Kidney	0	c <sub>m</sub> g	11
Minimal	0	6	2
Mild	0		3
Moderate	0	0	4
Marked	0	0	



### 88420 Males (Control)

- 4-1 Dilatation, Renal Tubule, Cortex, Minimal
- 10-1 Normal
- 28-1 Normal
- 46-1 Dilatation, Renal Tubule, Cortex, Mild
- 62-1 Regeneration, Renal Tubule, Minimal
- 76-1 Normal
- 104-1 Dilatation, Renal Tubule, Cortex, Mild
- 112-1 Normal
- 116-1 Normal
- 128-1 Regeneration, Renal Tubule, Minimal
- 136-1 Regeneration, Renal Tubule, Minimal
- 140-1 Normal
- 146-1 Normal
- 158-1 Normal
- 166-1 Normal
- 176-1 Regeneration, Renal Tubule, Minimal
- 184-1 Dilatation, Renal Tubule, Corticomed Jct, Minimal
- 190-1 Normal
- 198-1 Normal
- 216-1 Normal
- 222-1 Normal
- 226-1 Cyst, Cortex, Minimal
- 238-1 Normal



### 88420 Females (Control)

- 4-1 Normal
- 10-1 Dilatation, Renal Tubule, Cortex, Minimal
- 20-1 Normal
- 46-1 Normal
- 62-1 Normal
- 76-1 Dilatation, Renal Tubule, Corticomed Jct, Minimal
- 104-1 Regeneration, Renal Tubule, Minimal
- 112-1 Normal
- 116-1 Normal
- 128-1 Normal
- 136-1 Normal
- 140-1 Normal
- 146-1 Normal
- 158-1 Normal
- 166-1 Dilatation, Renal Tubule, Cortex, Minimal
- 176-1 Regeneration, Renal Tubule, Minimal
- 184-1 Normal
- 190-1 Dilatation, Renal Tubule, Corticomed Jct, Minimal
- 198-1 Normal
- 216-1 Regeneration, Renal Tubule, Minimal
- 222-1 Normal
- 238-1 Dilatation, Renal Tubule, Cortex, Minimal



### 31381 Males (Mid)

8-1 - Regeneration, Renal Tubule, Minimal

12-1 - Polycystic Kidney, Minimal

18-1 - Dilatation, Renal Tubule, Cortex, Mild

32-1 - Normal 48-1 - Normal

64-1 - Regeneration, Renal Tubule, Minimal

72-1 - Polycystic Kidney, Minimal 74-1 - Polycystic Kidney, Minimal

Regeneration, Renal Tubule, Minimal 92-1 - Dilatation, Renal Tubule, Cortex, Minimal Regeneration, Renal Tubule, Minimal

100-1 - Dilatation, Renal Tubule, Cortex, Minimal

106-1 - Polycystic Kidney, Minimal

Dilatation, Renal Tubule, Cortex, Minimal

114-1 - Polycystic Kidney, Mild
Dilatation, Renal Tubule, Cortex, Minimal
Regeneration, Renal Tubule, Minimal

144-1 - Dilatation, Renal Tubule, Cortex, Minimal Regeneration, Renal Tubule, Minimal

168-1 - Polycystic Kidney, Minimal

174-1 - Normal 194-1 - Normal

206-1 - Polycystic Kidney, Minimal Cyst, Cortex, Minimal

214-1 - Normal

228-1 - Polycystic Kidney, Minimal Regeneration, Renal Tubule, Minimal

240-1 - Dilatation, Renal Tubule, Cortex, Minimal



### 31381 Females (Mid)

8-1 - Dilatation, Renal Tubule, Corticomed Jct, Minimal

12-1 - Dilatation, Renal Tubule, Cortex, Minimal

18-1 - Normal

32-1 - Polycystic Kidney, Minimal

38-1 - Normal

48-1 - Polycystic Kidney, Minimal 64-1 - Polycystic Kidney, Minimal

Regeneration, Renal Tubule, Minimal

72-1 - Polycystic Kidney, Minimal

74-1 - Normal 100-1 - Normal

114-1 - Regeneration, Renal Tubule, Minimal

Dilatation, Renal Tubule, Corticomed Jct, Mild

144-1 - Polycystic Kidney, Minimal

Dilatation, Renal Tubule, Cortex, Minimal

168-1 - Normal 174-1 - Normal

194-1 - Polycystic Kidney, Minimal

Regeneration, Renal Tubule, Minimal 206-1 - Regeneration, Renal Tubule, Minimal

214-1 - Polycystic Kidney, Mild (Mineralization) Regeneration, Renal Tubule, Minimal

228-1 - Normal



### 82867 Males (High)

26-1 56-1	523 6139	Polycystic Kidney, Minimal Polycystic Kidney, Moderate	
70-1		Regeneration, Renal Tubule, Normal	Minimal
78-1	G.P	Polycystic Kidney, Mild	
118-1	~	Regeneration, Renal Tubule, Polycystic Kidney, Moderate	
124.1		Dilatation, Renal Tubule, Co Regeneration, Renal Tubule,	ortex, Minimal Minimal
		Polycystic Kidney, Moderate Regeneration, Renal Tubule,	Mild
		Polycystic Kidney, Marked Regeneration, Renal Tubule,	Mild
162-1	2004	Polycystic Kidney, Moderate Regeneration, Renal Tubule,	
200-1	F20	Polycystic Kidney, Marked	
212-1	68.	Regeneration, Renal Tubule, Polycystic Kidney, Marked	Minimal
		Regeneration, Renal Tubule, Polycystic Kidney, Moderate	Mild
Page		Regeneration, Renal Tubule,	Mild



## 82867 Females (High)

	22-1	690	Polycystic Kidney, Marked	
			Regeneration, Renal Tubula, Polycystic Kidney, Moderate	
	70-1	-	Regeneration, Renal Tubule, Polycystic Kidney, Minimal	Minimal
	78-1	•	Polycystic Kidney, Moderate	
			Regeneration, Renal Tubule, Polycystic Kidney, Moderate	
			Regeneration, Renal Tubule, Polycystic Kidney, Mild	Mild
			Regeneration, Renal Tubule, Polycystic Kidney, Marked	Minimal
			Regeneration, Renal Tubule, Polycystic Kidney, Mild	Mild
			Regeneration, Renal Tubule, Polycystic Kidney, Mild	Minimal
			Regeneration, Renal Tubule, Polycystic Kidney, Moderate	Minimal
			Dilatation, Renal Tubule, Co Regeneration, Renal Tubule	rtex, Minimal Minimal
el el	232-1	ena.	Polycystic Kidney, Minimal Regeneration, Renal Tubule,	
			a series a series of	1,1711THIGT



#### MEMORANDUM

FEB.28.1997

Received by Goy

TO: Rochelle W. Tyl, Ph.D.; RTI

Study Director

FROM: John Curtis Seely, D.V.M.; PATHCO W

Veterinary Pathologist

DATE: January 28, 1997

SUBJECT: Kidney Histopathology: Two-Generation Reproductive

Toxicity Evaluation of Wingstay 100 Administered in

the Feed to CD (Sprague-Dawley) Rats.

RTI Project No. 65C-6429-400; PATHCO 96-89

A microscopic review of the low dose F1 weanling (PND 21) male and female kidneys was conducted because in a previous review (Memorandum - dated January 16, 1997) treatment-related cystic renal lesions were observed in the high and mid dose animals.

During this review, similar treatment-related histopathologic lesions (Polycystic Kidneys) were present in some low dose animals. However, the incidence and severity of these lesions were less that in the mid dose animals confirming the strong dose-related nature of these lesions.

The incidence and severity of renal lesions in low dose animals and controls (previously reported) is as follows.

Histopathology Results From PND 21 Kidneys

#### MALE

DOSE	CONTROL	LOW
Kidney Exam. Normal Regeneration, RT* Dilatation, RT Inflammation Cyst Polycystic Kidney Minimal Hydronephrosis	23 14 4 4 0 1 0 0	25 14 3 5 1 2 1



#### FEMALE

Kidney Exam. 22 26	LOW
Normal 14 12 Regeneration, RT 3 6 Dilatation, RT 5 4 Cyst 0 2 Polycystic Kidney 0 5	26 12 6
Minimal 0 5	5

\*RT = Renal Tubule

The appearance of renal cysts associated with chemical exposure at the low dose were morphologically similar to those in the mid and high dose animals. The only exception was that, in several cases, cysts were solitary and smaller than those noted in the other dose levels. Additionally, 2 cases of medullary, renal tubule dilatation (M-102, F-86) and 1 case of medullary inflammation (M-208) were not coded as polycystic kidney but appeared to have a possible relationship with this condition. In these three cases, the location and appearance of the lesions had some similarity with those noted for polycystic kidney. However, cyst/cysts were not observed. It is possible that these lesions might represent early or precursor lesions to the cysts; however, further studies would have to be performed to confirm this observation.



#### 19640 Males (Low)

- 2-1 Normal
- 16-1 Polycystic Kidney, Minimal Regeneration, Renal Tubule, Minimal
- 24-1 Normal
- 30-1 Normal
- 34-1 Normal
- 52-1 Cyst, Cortex, Mild
- 66-1 Dilatation, Renal Tubule, Cortex, Minimal
- 80-1 Regeneration, Renal Tubule, Minimal
- 86-1 Normal
- 96-1 Normal
- 102-1 Dilatation, Renal Tubule, Medulla, Minimal
- 120-1 Dilatation, Renal Tubule, Cortex, Mild
- 124-1 Normal
- 132-1 Normal
- 142-1 Normal
- 148-1 Regeneration, Renal Tubule, Minimal
- 160-1 Normal
- 162-1 Dilatation, Renal Tubule, Cortex, Minimal
- 172-1 Dilatation, Renal Tubule, Cortex, Minimal
- 186-1 Hydronephrosis, Mild Cyst, Cortex, Mild
- 196-1 Normal
- 208-1 Inflammation, Medulla, Mild
- 210-1 Normal
- 230-1 Normal
- 234-1 Normal



## 19640 Females (Low)

		Normal
		Normal
		Normal
30-1	*120*	Regeneration, Renal Tubule, Minimal
34-1	410	Polycystic Kidney, Minimal
		Regeneration, Panal Tubula Winima
42-1	45.00	Polycystic Kidney, Minimal
		Regeneration, Renal Tubule, Minimal
		Normal
66-1	43	Dilatation, Renal Tubule, Cortex, Minimal
0 N - T	100	Regeneration. Renal Tubula Wisiasi
90-7	Alle	Dilatation, Renal Tubule, Medulla Minimal
30-7	Jun	Normat
		Normal
		Normal
124-1	-	Normal
132-1	eau	Dilatation, Renal Tubule, Cortex, Mild
126-1	429	kegeneration, Renal Tubula Minimal
749-7	400	Regeneration, Renal Tubule Minimal
T00-T	-	Cyst, Cortex, Minimal
162-1	rata	Normal
		Normal
186-1	wites	Normal
196-1	elique	Polycystic Kidney, Minimal
		Cyat, Cortex, Minimal
		Normal
210-1	em.	Polycystic Kidney, Minimal
230-1	440	Dilatation, Renal Tubula Cortar Minimal
234-1	-	Polycystic Kidney, Minimal
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